REMARKS/ARGUMENTS

Claims 1-13 and 16-22 are currently pending the present application. Applicants hereby amend claims 1-11, 13, 16-18 and 20-22, and cancel claim 12. Following entry of the current amendment, claims 1-11, 13 and 16-22 will be pending in the present application. The Examiner has rejected claims 1-13 and 16-22, and applicants address each of the Examiner's comments in the order made.

Support for the amendment to claim 1 may be found in the published application at paragraphs 8-9, 11 and 15-17. Claims 2-11 and 13 are amended for consistency with claim 1 from which they depend, and support may be found in the published application at paragraph 17. Support for the amendment to claim 16 may be found in the published application at paragraphs 9 and 12. Support for the amendment to claim 18 may be found in the published application at paragraph 12. Claims 17, 20 and 22 are amended to correct minor typographical errors, and claim 21 is amended for consistency with claim 16 from which it depends.

1. The Examiner has rejected claims 1-6, 11 and 13 pursuant to 35 USC 101 as allegedly directed to non-statutory subject matter. The Examiner asserts that the claims do not distinguish the claimed C1 inhibitor as it exists naturally, but suggests that the claims should be amended to recite "isolated" or "recombinant."

Applicants have amended claims 1-11 and 13 to recite "a recombinant C1 inhibitor," as suggested by the Examiner. Applicants submit that in light of the amendment, this ground of rejection should be withdrawn.

2. The Examiner has rejected claims 1-13 and 16-22 pursuant to 35 USC 112, first paragraph, as allegedly not being enabled by the specification. The Examiner asserts that the specification, while being enabling for a C1 inhibitor whose circulatory half-life is changed by an *in vitro* O-linked carbohydrate modification, or for a method of such *in vitro* modification, does not enable any method for changing the circulatory half-life of a C1 inhibitor *in vivo*, as broadly claimed.

Applicants have amended independent claim 1 to recite that the O-linked carbohydrate modification is "carried out by *in vitro* incubation with an enzyme preparation comprising one or more O-linked carbohydrate modifying enzymes or *in vivo* by co-expression of the C1 inhibitor with one or more O-linked carbohydrate modifying enzymes in a cell line or a

non-human transgenic animal." Furthermore, applicants have amended claim 16 to recite that the removal of the one or more non-sialylated O-linked carbohydrates from the glycoprotein is carried out "by *in vitro* incubation with an enzyme preparation comprising one or more enzymes capable of removing the one or more non-sialylated O-linked carbohydrates or *in vivo* by co-expression of the glycoprotein with one or more enzymes capable of removing the one or more non-sialylated O-linked carbohydrates in a cell line or a non-human transgenic animal."

The Examiner asserts that because the specification provides working examples only of *in vitro* modification of the O-linked carbohydrates, one of skill in the art would not have been able to practice the invention using any method of *in vivo* modification of the glycoprotein without "undue experimentation." Applicants submit that a working example of a particular embodiment (*e.g.*, *in vivo* modification by co-expression of a glycoprotein and an O-linked carbohydrate modifying enzyme in a cell line) is not required for enablement. *See* MPEP 2164.02. In the present case, one skilled in the art at the time of the invention would have readily appreciated the correlation between the description of *in vitro* modification of the O-linked carbohydrate moieties on the C1 inhibitor provided in the examples and the description of *in vivo* modification in cell culture systems or in a non-human transgenic animal through co-expression of the glycoprotein (*e.g.*, a C1 inhibitor) and one or more O-linked carbohydrate modifying enzymes, as described in the specification (*e.g.*, paragraphs 8-9 of the published application), and as presently claimed. That the particular enzymes described in the examples may have specificity for a variety of substrates is not of particular importance to the present inquiry. Applicants do not claim a specific modulation of the half-life *in vivo*. Moreover, one skilled in the art could readily determine the extent to which a glycoprotein's half-life has been modified by pharmacokinetic analysis, as described in example 3 of the specification.

Furthermore, applicants' current amendments recite "*in vivo* [modification] by co-expression ... in a cell line or a non-human transgenic animal." Therefore, the Examiner's concerns regarding the unpredictability of specific direct modulation of the half-life of a glycoprotein *in vivo* for therapeutic purposes, or the unpredictability of gene or enzyme therapy in humans, are allayed. One skilled in the art would appreciate that a glycoprotein could be modified by co-expression *in vivo* in a cell line or non-human transgenic animal, and that such

modified glycoproteins would be useful for, *e.g.*, intravenous administration as described in example 3 of the specification.

Because all other pending claims depend directly or indirectly from amended claims 1 and 16, applicants respectfully submit that, based on the foregoing, the rejection under 35 USC 112, first paragraph, should be withdrawn.

3. The Examiner has rejected claims 1-13 and 16-22 pursuant to 35 USC 103(a) as being unpatentable over Paulson et al (WO 98/31826), Schoenberger et al. (FEBS 314: 430-434 (1992)), Wolff et al. (Protein Expression and Purification 22: 414-421 (2001), and Glaser et al. (WO 92/03149) for the reasons of record set forth in the Office Action of April 19, 2006.

In the Office Action of April 19, 2006 the Examiner asserts that Paulson teaches increasing plasma circulatory half-life of therapeutic proteins by modification of both N- and O-linked oligosaccharides of recombinant glycoproteins. However, the Examiner acknowledges that "Paulson does not teach C1-INH and the importance of O-glycosylation." *See* paragraph bridging p. 7-8 of the 4-19-06 Office Action. The Examiner further asserts that Schoenberger teaches C1 inhibitor and the characterization of the carbohydrate moieties, as well as removal of sialic acid from native molecules. *See* p. 8, ¶ 2 of the 4-19-06 Office Action. The Examiner also asserts that Wolff teaches production and purification of recombinant C1 inhibitor and identifies the glycosylation sites in the human protein. *See* p. 8, ¶ 3 of the 4-19-06 Office Action. Finally, the Examiner asserts that Glaser teaches a method of treating thrombotic disease using a therapeutic protein that has been modified in the sugar residues of the O-linked glycosylation domain, including deletion of sugar moieties. *See* p. 8, ¶ 4 of the 4-19-06 Office Action. The Examiner concludes that it would have been obvious for one of ordinary skill in the art to use scialylation of a recombinantly produced C1 inhibitor to increase half-life in plasma circulation for therapeutic purposes, and that one would have been motivated to do so in order to treat disease associated with reduced C1 inhibitor activity. *See* p. 8, ¶ 5 of the 4-19-06 Office Action.

With reference first to independent claim 1, which is directed to a recombinant C1 inhibitor whose plasma circulatory half-life has been changed by modification of an O-linked carbohydrate. Applicants submit that the proper inquiry is whether one skilled in the art as of the priority date of the application would have found it obvious to modify an O-linked carbohydrate

on a C1 inhibitor in order to change the plasma circulatory half-life. The answer, based on the cited references, is clearly no.

Paulson, as the Examiner acknowledges, does not discuss C1 inhibitor, nor does Paulson recognize the importance of O-linked carbohydrate modification. One skilled in the art, seeking to change the plasma half-life of C1 inhibitor, would not have been guided by the discussion of Paulson to arrive at the claimed invention because neither the protein nor the importance of O-linked carbohydrate modification is described. Neither Schoenberger nor Wolff does anything to cure this deficiency because neither of these references discusses changing plasma circulatory half-life. Schoenberger describes investigations into the characteristics of the carbohydrate chains of the C1 inhibitor and of a de-sialylated C1 inhibitor. *See* p. 431, col. 2, 1st full paragraph. There is no discussion of changing plasma circulatory half-life by modification of an O-linked carbohydrate, and as such, one of skill in the art would not have been guided in that direction by the Schoenberger reference. Similarly, Wolff recognizes that recombinantly produced C1 inhibitors may play a role in treating hereditary deficiencies of such protein, but describes only an expression vector system for mass producing biologically active human recombinant C1 inhibitor. *See, e.g.*, p. 414, col. 1, 1st paragraph. The identification of glycosylation sites, as referred to by the Examiner, does nothing to direct a person of skill in the art to the importance of modifying an O-linked carbohydrate as a means of changing the plasma circulatory half-life, as claimed by applicants. Finally, Glaser discusses a method of treating thrombotic disease and identifies that one may increase "the in vivo circulating half life of a thrombomodulin analog ... [by] removing ... sugar moieties in the 6 EGF-like domains." *See* p. 4, lines 35-38. However, these domains are distinct from the "O-linked glycosylation" domain. *See* p. 11, lines 33-34. Therefore, one of skill in the art would not have been motivated by the disclosure of Glaser to modify O-linked carbohydrates to achieve a change in plasma circulatory half-life, as claimed by applicants.

In summary, none of the four cited references, either alone or in any combination, would have led a person of skill in the art at the priority date of the application to the conclusion that modification of an O-linked carbohydrate on a recombinant C1 inhibitor would change its plasma circulatory half-life. Therefore, claims 1-11 and 13 would not have been obvious to one

of skill in the art as of the priority date of the application, and applicants submit that the rejection under 103(a) regarding these claims should be withdrawn.

With reference next to independent claim 16, which is directed to a method for extending blood circulatory half-life of a glycoprotein or of a glycoprotein comprising compound via the removal of one or more non-sialylated O-linked carbohydrates from the glycoprotein. Applicants submit that here the proper inquiry is whether one skilled in the art as of the priority date of the application would have found it obvious to remove a non-sialylated O-linked carbohydrate from a glycoprotein in order to extend the blood circulatory half-life. Again, the answer, based on the cited references, is clearly no.

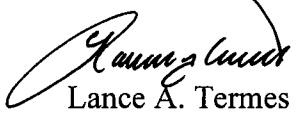
As the Examiner acknowledges, Paulson does not recognize the importance of O-linked carbohydrate modification to extending the blood circulatory half-life of a glycoprotein. Moreover, Paulson discusses methods for sialylation of glycoproteins, not the removal of non-sialylated O-linked carbohydrates. One skilled in the art, seeking to extend the blood circulatory half-life of a glycoprotein, would not have been guided by the discussion of Paulson to arrive at the claimed invention because Paulson is focused on the addition of sialic acid to saccharide groups and makes no mention of removing non-sialylated carbohydrates, let alone O-linked carbohydrates. Schoenberger does nothing to cure this deficiency because Schoenberger does not discuss extending blood circulatory half-life of glycoproteins. The discussion in Schoenberger regarding the removal of sialic acid, which is referred to by the Examiner in the April 19, 2006 Office Action, makes no mention of removing the non-sialylated O-linked carbohydrates, as claimed by applicants. In contrast, Schoenberger expressly "confirm[s] the presence of O-glycosidic linked sugars" in the desialylated C1 inhibitor. *See* p. 432, col. 1, § 3.3.1. As described above, Wolff recognizes the importance of C1 inhibitors in treating hereditary deficiencies of such protein, but describes only an expression vector system for mass producing biologically active human recombinant C1 inhibitor. *See, e.g.*, p. 414, col. 1, 1st paragraph. The identification of glycosylation sites, as referred to by the Examiner, does nothing to direct a person of skill to the importance of removing a non-sialylated O-linked carbohydrate as a means of extending the blood circulatory half-life, as claimed by applicants. Similarly, Glaser does nothing to cure the deficiencies identified above. Glaser discusses a method of treating thrombotic disease and identifies that one may increase "the <u>in vivo</u> circulating half life

of a thrombomodulin analog ... [by] removing ... sugar moieties in the 6 EGF-like domains." *See* p. 4, lines 35-38. However, as described above, these domains are distinct from the "O-linked glycosylation" domain. *See* p. 11, lines 33-34. Therefore, one of skill in the art would not have been motivated by the disclosure of Glaser to remove non-sialylated O-linked carbohydrates to extend the blood circulatory half-life of a glycoprotein, as claimed by applicants.

In summary, none of the four cited references, either alone or in any combination, would have led a person of skill in the art at the priority date of the application to the conclusion that removal of a non-sialylated O-linked carbohydrate from a glycoprotein would extend the blood circulatory half-life. Therefore, claims 16-22 would not have been obvious to one of skill in the art as of the priority date of the application, and applicants submit that the rejection under 103(a) regarding these claims should be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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